REMARKS

Claim 1 has been amended for clarity and to resolve some issues raised in the outstanding Office action. First, "an isolated single copy of a target nucleic acid" has been changed to what is apparently a clearer term, "an isolated target nucleic acid molecule." Applicants believe that the preposition "in" is actually correct, since the region that is to be interrogated is in this molecule. The phrase "no more than 1,500 bases" has been changed to "as little as 1,500 bases" which is clearly supported by the specification. This obviates the rejection under 35 U.S.C. § 112, paragraph 1.

As to 35 U.S.C. § 112, paragraph 2, the interrogating step has been added to the preamble so that it now matches the final sentence of the claim. The phrase "target nucleic acid molecule" has been used throughout, applicants believe, consistently. This takes care of the objections in the last two paragraphs on page 4 of the Office action.

The other amendment to claim 1 is to require that the first and second particulate labels each contain at least two fluorophores that emit light of different wavelengths. Two fluorophores is supported by claim 2, now canceled. Fluorophores of different wavelengths is supported in paragraph 28.

Thus, no new matter has been added to claim 1.

Claim 2 has been canceled as now redundant and claim 3 has been canceled as unnecessary. Claims 5, 6 and 7 have been amended to conform to the terminology of claim 1. Claims 8-14 have been canceled to expedite prosecution and claim 15 has been amended to depend from claim 1 rather than from canceled claim 8.

No new matter has been added.

Applicants respectfully request the Examiner to exercise her discretion to enter the proposed amendment although made after final. First, the insertion of the limitations of claim 2 into claim 1 should be entered since claim 2 has presumably already been considered and thus no further consideration is required. Second, the other amendments to claim 1 are directly in response to formal rejections made by the Examiner and correct the defects that the Examiner has identified, as have the amendments to claims 5-7. In view of there being no earlier opportunity to make such amendments, it is believed proper to enter them now as placing the claims in a better position for allowance or appeal.

The Invention

The invention provides a method to pinpoint a region in a nucleic acid molecule that can be further interrogated as to its nature. For example, if one wishes to detect the presence of a SNP, this can be done with a very short probe because irrelevant regions which would bind to such a short probe can be ignored. This is because the invention method identifies the region to be interrogated. This is explained, for example, in paragraph 18 of the specification. Thus, the invention provides an efficient method to interrogate nucleic acid molecules, either one nucleic acid molecule at a time as permitted, but not mandated, in claims 1 and 4-6, or in a multiplexed assay as set forth in claim 7.

The Rejections Under 35 U.S.C. § 112

The rejection under the first paragraph of this section has been obviated by amendment and the objections to claims 1 and 8 have been obviated by amendment as well. As to the objections to claims 4-6 (and 11-13, which have been canceled), it is believed that the phraseology said first and

second oligonucleotides or first and second identification probes does have support because straightforward English grammar permits this telescoping of the language to refer to first and second forms previously articulated. Similar comments apply to the rejection of claim 7. If the Office prefers, more prolix wording may be substituted; however, this is believed counterproductive.

The Art Rejections

First, applicants appreciate the withdrawal of the rejections over the art previously made.

The Rejections for Anticipation

Claims 1, 4-5, 7-8, 11-12, 14-15 and 17 were rejected as assertedly anticipated by Cai (WO01/90418). Claims 8, 11-12 and 14 have been canceled.

Applicants are certain that the Office is aware that in order for anticipation to be found, each and every limitation of the claim must be found explicitly or inherently in a single prior art document, and elements that are connected in the claim must be connected in the document. *Hyatt v. Dudas*, 83 USPQ2d 1373 (Fed. Cir. 2007). In the present case, the claims as amended are clearly free of this rejection for several reasons.

First, the limitations of claim 2 have been incorporated into claim 1, from which all other claims depend. As claim 2 was not included in this rejection, it follows that claim 1 is now also free of it. The requirement that the labels each comprise first and second fluorophores – *i.e.*, that they are combinatorially labeled – is not found in Cai. Also, this is true for a reason, not just because Cai forgot to mention it, which will be elaborated on in connection with the rejection under § 103 below.

Second, there is no separate step in Cai of interrogating a region that has been identified using two separate labels. The binding of the labels themselves in Cai constitutes what amounts to interrogation. The method of the present invention has two steps. Cai's method has only one.

Third, and importantly, there has always been a limitation in claim 1 that the pair of first and second particulate labels be detected as separate points in space. Cai fails to disclose this feature.

The Office appears to believe that this feature is disclosed by virtue of observation of the bound labels using an ultrasensitive luminescence confocal microscope (bottom of page 6 of the Office action). However, this is not the way a confocal microscope works. Rather, the single nucleic acid molecule is observed as a single pixel as it diffuses in and out of a very small detection volume. The single pixel is in turn interrogated for its components. Thus, as described in Cai itself, at page 14, beginning at line 24, the fluorescence is collected and passes through a beam-splitter and is then spectrally split with the dichroic beam-splitter into two sensitive photon-counting detectors. Thus, as Cai itself describes, the light generated by more than one probe is collected as a single beam and then, subsequently, split into its component wavelengths. This is clearly not the same as observing the presence or absence of each member of any pairs as separate points in space.

Cai, in fact, teaches away from observing these as single points in space, since there is no need to identify a region which is then going to be interrogated, the only thing Cai wants to know is which probes have been bound to the target molecule.

What Cai is doing, then, is not identifying a region, but rather detecting the binding of multiple probes to the same nucleic acid molecule where the detection does not identify them in space individually, but simply registers their presence by detecting the presence of the signal from each of them in a single emitted light beam.

Thus, for the reasons set forth above, Cai fails to anticipate the present claims.

These claims were also rejected under 35 U.S.C. § 102(e) as anticipated by Cai (US2006/0008799) which claims priority to provisional application 60/206512 filed 22 May 2000. This is the same application as the above cited PCT document. The reasons this rejection may be withdrawn are the same as those set forth above. It is assumed that this rejection was made to push back the date behind which applicants would need to swear, should the invention not have been distinguishable from these documents.

The Rejections for Obviousness

Claims 2-3 and 9-10 were rejected as assertedly obvious over the same Cai PCT publication in view of Kauvar (WO00/14545). Claims 9 and 10 have been canceled. The Office argues that it would have been obvious to use the combinatorial beads of Kauvar in place of the monochromatic beads of Cai.

First, Cai does not disclose, anticipate or suggest the method of the present claims, regardless of the labels used. Cai actually teaches away by disclosing methods of detection which detect emissions as a single pixel which is only subsequently separated into component wavelengths.

Second, it makes no sense to use the combinatorial beads of Kauvar in the Cai approach because to do so would only complicate the assay. It would be necessary to further separate the single pixel emitted from the sample into a multiplicity of additional wavelengths representing each and every fluorophore contained in each and every particle. Because the hue emitted by a combinatorial particle is determined by the ratio of the fluorophores that compose it, and because the particles are not separately visualized in Cai, there is no purpose to be served by generating a

characterizing hue in this manner. In the present invention, combinatorial labels permit the multiplexing of claim 7. Attempting to use combinatorial beads to multiplex Cai's method would render it hopelessly cumbersome.

Accordingly, this basis for rejection may also be withdrawn.

Claims 6 and 13 were rejected as assertedly obvious over the Cai PCT publication in view of Nie (U.S. 6,060,242). Nie is cited simply for disclosing formation of a triplex, a feature not necessary for patentability.

Claim 16 was rejected as obvious over the Cai PCT publication in view of Spies (U.S. 5,736,334). Spies is cited for disclosing detection of a hepatitis B viral DNA, again a feature not needed for patentability.

The same series of rejections are based on combining Kauvar, Nie or Spies with the equivalent Cai U.S. patent publication, and may be withdrawn for the same reasons as those set forth above.

Conclusion

The invention method as now claimed differs from the method of the Cai primary documents for at least three reasons. First, Cai does not detect two labeled oligonucleotide-labeled probes as separate points in space. The confocal microscopy technique described in Cai detects a single light beam from a DNA molecule containing one or more probes and then subsequently splits this into components. The probes are not seen as separate points in space.

Second, the foregoing is important, because all Cai wants to know is which probes do and which probes do not bind to the target nucleic acid molecule. Applicants' method, on the other hand, requires both identifying a region to be further interrogated by detecting labeled probes as

separate points in space and then further interrogating the region so identified. As noted above, this permits, for example, efficient identification of SNP's by using relatively short probes since only the region where the SNP is to be found need be assessed.

Third, as the claims as amended now require the use of combinatorial beads as labels, an inclusion which would at best complicate the interpretation of Cai's results, and prevent efficient multiplexing thereof.

In short, Cai teaches away from the method claimed herein.

Accordingly, applicants respectfully request that the proposed amendment be entered and that claims 1, 4-7 and 15-17 be passed to issue.

If minor issues remain that could be resolved by phone, a call to the undersigned would be appreciated.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 388512011000.

Respectfully submitted,

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